

Crisis of emerging antibiotic resistances mirroring that of the COVID-19 in the age of globalisation

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During the past 100 years, humans were affected by several severe pandemics that caused millions of deaths, including influenza, acquired immune deficiency syndrome (AIDS), severe acute respiratory syndrome (SARS), Middle Eastern respiratory syndrome (MERS), Ebola, Zika. The newest, COVID-19, first targeted China, then other Asian countries, the Middle East and Europe, and rapidly reached all continents, being recognised as a pandemic by the World Health Organization on 11 March 2020. Ancient epidemics spread slowly at the speed of ships and coaches, and were halted by quarantine measures such as in the Hoffman Island immigration station in New York City during the late 19th century. New pandemics such as the community-acquired respiratory syndrome COVID-19 disseminate rapidly at the international level, which is enabled by human crowding in housing and during big social events, and by massive use of rapid travel by air [1]. In 2018, the total number of airplane passengers was estimated to be 4.3 billion.

The worldwide spread of emerging antibiotic resistances mirrors that of the SARS-Cov-2: unapparent carriers, crowding, low hygiene and rapid travel. However, whereas for COVID-19 no specific and active antiviral drug is available, in the case of antibiotic resistance, the opposite is occurring: we are losing the most valuable life-saving drugs – antibiotics. The most important evolutions of antibiotic resistance occurred in Gram-negative bacteria, mainly in Enterobacteriaceae (e.g., *Escherichia coli*, *Klebsiella pneumoniae*, *Salmonella* spp). These bacterial species can act as pathogens, causing community- and hospital-acquired infections [2]. In addition, their carriage in the gut flora of humans and animals is a source of the silent spread of resistance genes. The emergence of extended-spectrum β -lactamases (ESBLs) (CTX-M type), in particular in community-acquired *E. coli*, was extensively reported in the early 2000s [3]. These enzymes confer resistance to all β -lactams except carbapenems. Their genes are easily transmissible among Enterobacteriaceae through plasmids and are often associated with multidrug resistance to other antibiotic families such as fluoroquinolones and aminoglycosides. In 2001, we reported that CTX-M-15, which originally was recovered from an *E. coli* isolate from India,

became the main ESBL determinant worldwide [4]. CTX-M-14 is another ESBL that was first reported in Southern China in 1998 at a very high rate in the Guangzhou region, the assumed epicentre, from which it spread worldwide [4]. The spread of these CTX-M-producing enterobacterial strains to Europe by colonised or/and infected patients and travellers from areas where they emerged is widely documented [3]. The high emergence of CTX-M-producing enterobacteria in their original geographical locations is a result of several factors including enrichment of the resistant clones by misuse or overuse of antibiotics, insufficient sewage treatment and low sanitary infrastructure. As an example, resistance to expanded-spectrum cephalosporins in *E. coli* is estimated to be around 60–80% in India, compared with 8% in Switzerland [5, 6]. Those numbers may underestimate the true prevalence of ESBLs, since ESBL producers may also confer susceptibility to several expanded-spectrum cephalosporins.

The second most important resistance determinants widely identified in Enterobacteriaceae are carbapenemases, mainly found in *K. pneumoniae* [7, 8]. They confer resistance to virtually all β -lactams and are associated with many other resistance determinants. One of the most widespread carbapenemases is the KPC enzyme (*Klebsiella pneumoniae* carbapenemase). First reported in the US, it has since been identified worldwide [7, 8]. In Europe, KPC-producing enterobacteria are considered to be endemic in Italy and Greece [7, 8]. In Switzerland, most of the KPC producers identified at the National Reference Centre for Emerging Antibiotic Resistance (NARA) originated from patients who were hospitalised in Italy or Greece. In 2008, a novel carbapenemase (NDM-1) was identified in Sweden from a patient returning from New Delhi [7]. A further study revealed NDM producers in the UK, India and Pakistan [7]. Now NDM is known to be widespread in South East Asia from where it disseminates worldwide [8]. The spread of NDM producers is of great concern: NDM-5-producing and clonally-related *E. coli* isolates identified in Switzerland and Germany were even resistant to the latest developed antibiotic combination aztreonam/avibactam (P. Nordmann personal communication).

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In 2002, we identified the first case of a producer of the carbapenemase OXA-48 from a Turkish *E. coli* isolate [9]. Since that time, numerous studies have shown the widespread dissemination of OXA-48-like producers, mostly being community-acquired *E. coli* in Northern Africa, the Middle East and Europe [8]. OXA-48-like enzymes are the most prevalent carbapenemases in Switzerland. We recently identified OXA-244, an OXA-48-like *E. coli* spreading in Switzerland and Germany ([10] and P. Nordmann personal communication).

As for COVID-19, frequent travel, in particular by air, causes rapid global spread of resistance genes. The main air traffic routes mutually link Asia with Europe and the Americas. Asia's emerging economies create heavy antibiotic consumption in medicine and agriculture, which, combined with crowding in megacities of >10 million inhabitants, close contacts between humans and animals as in open markets, and deficits in public health infrastructure result in the emergence of high rates of resistance to antibiotics.

The current spread of resistance genes worldwide, mostly from developing countries, may soon lead to difficult situations similar to that observed now for COVID-19. In contrast to SARS-Cov2, which manifests by a sudden increase of severe atypical respiratory symptoms and monitored on a daily basis in each country worldwide, the spread of resistance genes is silent, mostly in non-symptomatic carriers since it is not associated with specific virulence traits. However, once in the population, resistance genes are difficult or impossible to control or eradicate. They remain in commensal bacteria in humans and animals, and represent a source for further outbreaks, in particular in community-acquired diseases. A main factor driving the spread of resistance genes relates to the ubiquity of *E. coli*. This species is a major source of bacterial infections in humans. However, it is also an important commensal bacterium of the gut flora, hence representing a massive source of hidden spread of antibiotic resistance genes. Many *E. coli* clones exchange between animals and humans and facilitate the transfer of antibiotic resistance genes either directly via the food chain or in the environment. We are constantly observing the accumulation of novel resistance traits in Gram-negative bacteria, which should best be identified in reference centres such as the NARA for Switzerland. They are maintained in the environment or the gut flora of humans and animals by the selective pressure linked to the use of antibiotics. Co-selection of resistance to new antibiotics even by old, narrow spectrum antibiotics occurs due to multi-resistance plasmids.

Similar to the COVID-crisis, control of emerging antibiotic resistance genes requires early detection, rapid diagnosis, early intervention and development of novel antimicrobial agents. Epidemiological surveillance at the local level for emerging resistance at the molecular and biochemical levels is therefore required. The NARA at the Fribourg University fulfils this surveillance role in Switzerland. Rapid diagnostic tests for antibiotic resistance, such as those developed for identification of ESBLs and carbapenemases, are crucial to prevent their spread and to optimise antibiotic therapy and rapid interventions such as isolating infected or carriers in hospital settings [11, 12].

On a global level, similar to COVID-19, exchange of information on the emergence of antibiotic resistance and multi-resistance in due time is crucial for efficient measures to avoid spreading in new settings. New antibiotic resistances appear to originate largely from Asian countries with increasing wealth and intensive use of antibiotics in medicine and agriculture, facilitated by over-the-counter sales. However, exchange of resistance data and of resistant strains for reference purposes is not satisfactory on a global level.

Antibiotics are a central pillar of the infrastructure of our health system and are among the most important lifesaving medicines. Resistance spreads globally and requires a global strategy to ensure efficient treatments of infectious diseases in the future. COVID-19 has revealed the devastating effect of a pandemic against which therapeutic and preventive medicines were lacking. Staying a step ahead of pan-drug-resistance, which would make it impossible to treat infections, effective strategies in tracing antibiotic resistance, rapid and specific diagnostics, compulsory antibiotic stewardship rules and new efficient antibiotics against infectious diseases are urgently needed.

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